

B5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/12237 A2

(51) International Patent Classification⁷: **C07D 471/04, 519/00 // (C07D 471/04, 239:00, 221:00) (C07D 519/00, 471:00, 471:00)**

(21) International Application Number: **PCT/US01/22001**

(22) International Filing Date: **12 July 2001 (12.07.2001)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60/223,084 4 August 2000 (04.08.2000) US

(71) Applicant (*for all designated States except US*): **WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).**

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BEYLIN, Vladimir Genukh [US/US]; Pfizer PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). LEE, Richard, Jungkyu [US/US]; Pfizer Holland Chemical Development, 188 Howard Avenue, Holland, MI 49423 (US). MARLATT, Mark, Eugene [US/US]; Pfizer PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).**

(74) Agents: **FEDERMAN, Evan, J. et al.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US).**

(81) Designated States (*national*): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**

(84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/12237 A2

(54) Title: **PROCESS FOR PREPARING 2-(4-PYRIDYL)AMINO-6-DIALKYLOXYPHENYL-PYRIDO[2,3-D]PYRIMIDIN-7-ONES**

(57) Abstract: **Process for preparing 2-pyridylamino-pyrido[2,3-d]pyrimidines of Formula (II) wherein Ar is aryl, R' and R'' are hydrogen, alkyl, alkoxy, or phenyl, and R² is alkyl.**

-1-

PROCESS FOR PREPARING 2-(4-PYRIDYL)AMINO-6-
DIALKYLOXYPHENYL-PYRIDO[2,3-D]PYRIMIDIN-7-ONES

FIELD OF THE INVENTION

5 This invention concerns a chemical process for preparing
pyrido[2,3-d]pyrimidines having a pyridylamino group at the 2-position.

BACKGROUND OF THE INVENTION

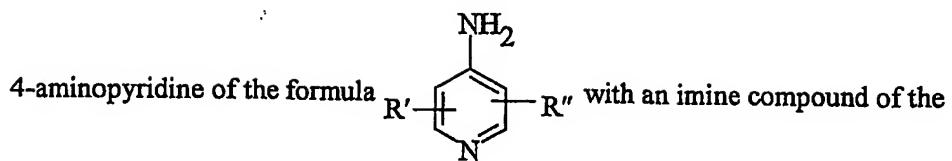
United States Patent No. 5,733,914 (which is incorporated herein by
reference) describes a series of pyrido[2,3-d]pyrimidines that inhibit protein
10 tyrosine kinase mediated cellular proliferation. The compounds are anti-
angiogenic agents, and as such are useful for treating cancer, particularly leukemia
and breast cancer. The 5,733,914 patent teaches that a particularly preferred group
of compounds are substituted at the 2-position with an arylamino group, and that
the aryl moiety can be a pyridyl group. 2-(4-Pyridyl)amino-
15 pyrido[2,3-d]pyrimidines appear to be a preferred group of compounds because of
their metabolic stability and tyrosine kinase selectivity. One such compound,
namely 2-(pyridin-4-ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-
pyrido[2,3-d]pyrimidin-7-one, is currently being studied as a possible clinical
candidate for treating cancer.

20 Because these compounds are commercially viable anticancer agents, the
need exists for a synthetic process that affords the desired compound in high
purity and satisfactory yields. This invention provides a commercially viable
process for making such pyridylamino-pyrido[2,3-d]pyrimidines.

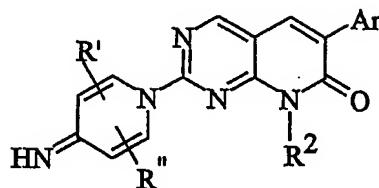
SUMMARY OF THE INVENTION

25 This invention provides a chemical process for preparing 2-(pyridin-4-
ylamino)-pyrido[2,3-d]pyrimidines comprising reacting a 4-aminopyridine with a
2-(4-imino-4H-pyridin-1-yl)-6-aryl-8-substituted-8H-pyrido[2,3-d]pyrimidine-
7-one. More particularly, the invention provides a process for reacting a

-2-

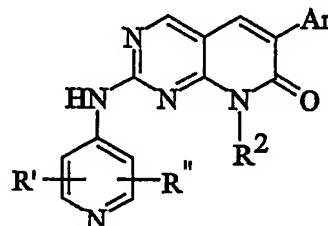


Formula I



I

in the presence of a base to provide a pyridylamino compound of Formula II



II

wherein:

R' and R'' independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, or C₁-C₆ alkanoyl;

R² is (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3;

heteroaromatic, cycloalkyl, C₁-C₆ alkanoyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, and C₂-C₆ alkynyl, where the alkyl, alkenyl, and alkynyl groups may be substituted by NR₅R₆, phenyl, substituted phenyl, thioalkyl, alkoxy, carboxy, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and

R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, substituted nitrogen, oxygen, and sulfur;

Ar is phenyl, substituted phenyl, or heteroaromatic; and the pharmaceutically acceptable salts thereof.

-3-

Preferably, R' and R" independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or phenyl.

It is also preferred that R² is (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; heteroaromatic, cycloalkyl, C₁-C₆ alkyl, and C₂-C₆ alkenyl, where the alkyl and alkenyl groups may be substituted by NR₅R₆, 5 phenyl, substituted phenyl, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 10 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur.

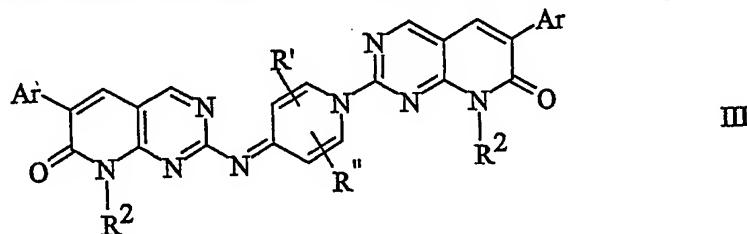
In a preferred embodiment, R' and R" both are hydrogen.

In another preferred embodiment, Ar is substituted phenyl and is more 15 preferably 3,5-di-C₁-C₆ alkoxyphenyl. Ar is most preferably 3,5-dimethoxyphenyl.

In another preferred embodiment, R² is C₁-C₆ alkyl.

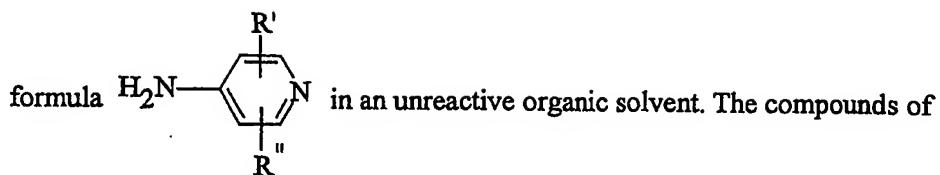
It is preferred that the compound of Formula II is 2-(pyridin-4-ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one.

In a further embodiment, the invention provides a process for preparing a 20 pyridylamino pyridopyrimidine compound of Formula II comprising reacting an aminopyridine with a dimer-like compound of Formula III



wherein Ar, R', R'', and R² are as defined above. Additionally, for a compound 25 of Formula III, R² can be hydrogen. The process comprises reacting the dimer-like compound of Formula III with a catalytic amount of an aminopyridine of the

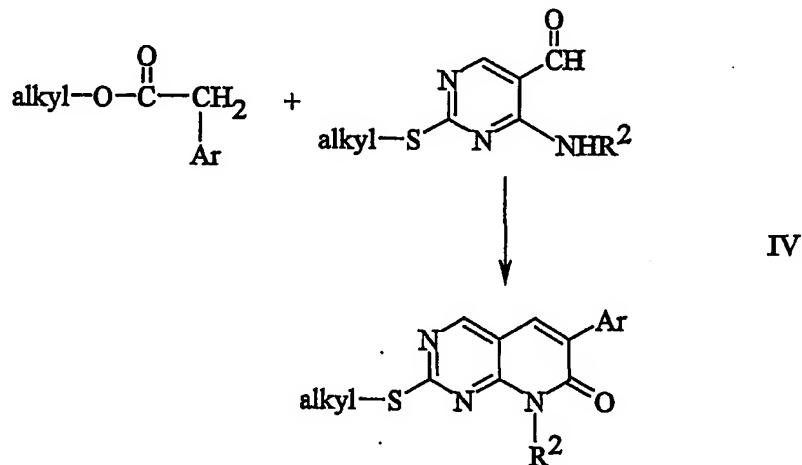
-4-



Formula III are provided as a further embodiment of the invention. These compounds are named as 2-{4-[(6-aryl-7-oxo-8-substituted-8H-pyrido[2,3-d]-pyrimidin-2-yl)-imino]-4H-pyridin-1-yl}-6-aryl-8-substituted-8H-pyrido[2,3-d]-pyrimidin-7-ones.

Also provided by this invention are new compounds defined by Formulas I and III above. These compounds are useful as starting materials or intermediates in the synthesis of the pyridylamino pyridopyrimidine compounds of Formula II.

In still a further embodiment, the invention provides a process for preparing a 2-alkylsulfanyl pyridopyrimidine of Formula IV comprising reacting an aryl acetic acid ester with a 2-alkylsulfanyl-4-alkylamino-pyrimidine-5-carboxaldehyde according to the following scheme:



wherein Ar and R² are as defined above. Additionally, for a compound of Formula IV, R² can be hydrogen.

The 2-alkylsulfanyl pyridopyrimidines of Formula IV are useful as intermediates in the synthesis of 2-(4-imino-4H-pyridin-1-yl)-pyridopyrimidines of Formula I.

-5-

DETAILED DESCRIPTION OF THE INVENTION

For purposes of the present invention, the terms "alkyl" and "C₁-C₆ alkyl" mean a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and include, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. The term "C₁-C₆ alkyl" includes within its definition the term "C₁-C₃ alkyl".

5 "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The terms "alkenyl" and "C₂-C₆ alkenyl" mean a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms and 1 double bond and includes ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like.

10 The terms "alkynyl" and "C₂-C₆ alkynyl" mean a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms and at least one triple bond. Typical C₂-C₆ alkynyl groups include propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like.

15 The terms "cycloalkyl" and "C₃-C₆ cycloalkyl" mean a cyclic hydrocarbyl group such as cyclopropyl, cyclobutyl, cyclohexyl, and cyclopentyl.

The terms "alkoxy" and "C₁-C₆ alkoxy" refer to the alkyl groups mentioned above binded through oxygen, examples of which include methoxy, ethoxy, isopropoxy, tert-butoxy, and the like.

20 The term "C₁-C₆ alkanoyl" refers to an alkyl group, as defined above, linked through a carbonyl, i.e., C₁-C₅

25
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{alkyl C-} \end{array}$$
 Such groups include formyl, acetyl, propionyl, butyryl, and isobutyryl. "Acyl" means an alkyl or aryl (Ar) group bonded through a carbonyl group

30
$$\begin{array}{c} \text{O} \\ \parallel \\ (-\text{C-}) \end{array}$$
 For example, acyl includes a C₁-C₆ alkanoyl, including substituted alkanoyl, wherein the alkyl portion can be substituted by NR₅R₆ or a carboxylic or heterocyclic group. Typical acyl groups include acetyl, benzoyl, and the like.

-6-

The alkyl, alkenyl, alkoxy, and alkynyl groups described above may be substituted. The substituent groups which may be part of the alkyl, alkenyl, alkoxy, and alkynyl groups are NR₅R₆, phenyl, substituted phenyl, thio(C₁-C₆)alkyl, C₁-C₆ alkoxy, carboxy, C₁-C₆ alkoxy carbonyl, cycloalkyl, and 5 a 5- to 7-membered carbocyclic ring or heterocyclic ring having 1 or 2 heteroatoms selected from nitrogen, substituted nitrogen, oxygen, and sulfur. "Substituted nitrogen" means nitrogen bearing C₁-C₆ alkyl or (CH₂)_nPh.

10 Examples of substituted alkyl groups thus include 2-aminoethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, 3-phenylbutyl, methylsulfanyl methyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, 3-cyclopropylpropyl, 3-morpholinopropyl, piperazinylmethyl, and 2-(4-methylpiperazinyl)ethyl.

15 Examples of substituted alkenyl groups thus include 2-diethylaminoethenyl, 3-amino-2-butenyl, 3-(1-piperazinyl)-1-propenyl, 3-hydroxy-1-propenyl, 2-(1-s-triazinyl)ethenyl, 3-phenyl-3-pentenyl, and the like.

20 Examples of substituted alkynyl groups include 2-methoxyethynyl, 2-ethylsulfanyethynyl, 4-(1-piperazinyl)-3-(butynyl), 3-phenyl-5-hexynyl, 3-diethylamino-3-butynyl, 4-chloro-3-butynyl, 4-cyclobutyl-4-hexynyl, and the like.

25 Typical substituted alkoxy groups include aminomethoxy, trifluoromethoxy, 2-diethylaminoethoxy, 2-ethoxycarbonylethoxy, 3-hydroxypropoxy, 6-carboxyhexyloxy, and the like.

30 Further, examples of substituted alkyl, alkenyl, and alkynyl groups include dimethylaminomethyl, carboxymethyl, 4-diethylamino-3-buten-1-yl, 5-ethylmethylamino-3-pentyn-1-yl, 4-morpholinobutyl, 4-tetrahydropyridinylbutyl-3-imidazolidin-1-ylpropyl, 4-tetrahydrothiazol-3-ylbutyl, phenylmethyl, 3-chlorophenylmethyl, and the like.

35 The term "Ar" refers to unsubstituted and substituted aromatic and heteroaromatic groups. Heteroaromatic groups have from 4 to 9 ring atoms, from 1 to 4 of which are selected from O, S, and N. Preferred groups have 1 or 2 heteroatoms in a 5- or 6-membered aromatic ring. Mono and bicyclic ring systems are included. Typical Ar groups include phenyl, 3,5-dimethoxyphenyl,

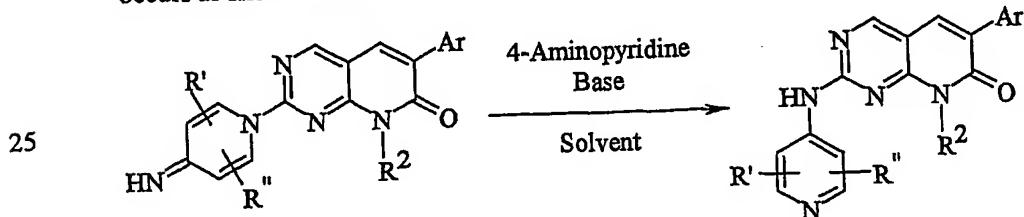
-7-

3-chlorophenyl, 2,6-dibromophenyl, pyridyl, 3-methylpyridyl, benzothienyl, 2,4,6-tribromophenyl, 4-ethylbenzothienyl, furanyl, 3,4-diethylfuranyl, naphthyl, 4,7-dichloronaphthyl, and the like.

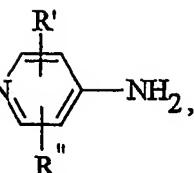
Preferred Ar groups are phenyl and phenyl substituted by 1, 2, or 3 groups independently selected from alkyl, alkoxy, alkanoyl, -CN, -NO₂, -COOR₈ (where R₈ is C₁-C₆ alkyl, or benzyl), -CF₃, and alkanoyloxy. Disubstituted phenyl is most preferred, and 3,5-disubstituted phenyl, such as 3,5-dimethoxyphenyl, is especially preferred.

Typical Ar substituted phenyl groups which are preferred thus include 2-aminophenyl, 3-chloro-4-methoxyphenyl, 2,6-dimethylphenyl, 2,6-diethylphenyl, 2-n-hexyl-3-fluorophenyl, 3-isopropoxypyhenyl, 4-chloromethylphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,6-dichlorophenyl, 4-(3-aminopropoxy)phenyl-, 2,6-difluorophenyl, 2-chloro-6-methylphenyl, 2,4,6-trichlorophenyl, 2,6-dimethoxyphenyl, 4-(diethylaminoethoxy)phenyl, 2-fluoro-3,5-dimethoxyphenyl, 2,6-dibromophenyl, 2,6-dinitrophenyl, 2,6-di-(trifluoromethyl)phenyl, 3-(dimethylaminoethyl)phenyl, 2,6-dimethylphenyl, 2,3,6-trimethylphenyl, 2,6-dibromo-4-methylphenyl, and the like.

The process of this invention is carried out by reacting the 2-(4-imino-4H-pyridin-1-yl)-pyrido[2,3-d]pyrimidine of Formula I, preferably as an acid addition salt such as the hydrochloride salt, with a 4-aminopyridine in the presence of a base and in an organic solvent to provide the corresponding 2-(pyridin-4-yl-amino)-pyrido[2,3-d]pyrimidine of Formula II. The reaction occurs as shown below:



-8-



The 4-aminopyridine used in the process has the formula $\text{N}(\text{R}')(=\text{N})\text{C}_6\text{H}_3(\text{R}'')\text{NH}_2$,

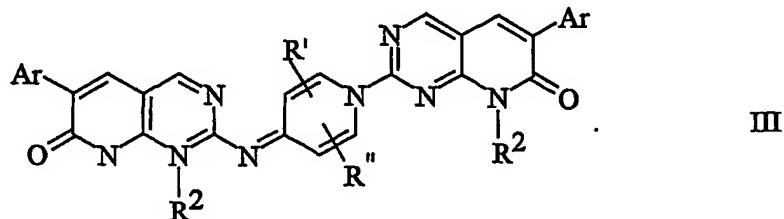
wherein R' and R'' are the same substituents on the 4-imino-1,4-dihydropyridine ring portion of the starting material. The starting pyridopyrimidine of Formula I and the base typically are used in approximately equimolar amounts, whereas the 5 4-aminopyridine generally is used in only a catalytic amount, for example from about 0.05 to about 0.5 equivalents relative to the pyridopyrimidine starting material.

“Base” as used herein means any inorganic compound that provides negative ions in solutions of water or polar organic solvents. Typical bases include 10 inorganic carbonates and bicarbonates such as potassium carbonate, sodium bicarbonate, potassium bicarbonate, and sodium bicarbonate. Hydroxides such as sodium hydroxide and potassium hydroxide also can be used.

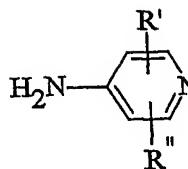
The process of this invention is generally carried out in an unreactive 15 organic solvent. The particular solvent is not critical. Typical solvents commonly used include dimethylsulfoxide, dimethylformamide, acetonitrile, tetrahydrofuran, glyme, diglyme, sulfolane, and N-methylpyrrolidinone (NMP).

The reaction generally is substantially complete within about 24 hours to 20 about 60 hours when carried out at a temperature of about 30°C to about 190°C. While the exact temperature at which the reaction is conducted is not critical, heating above room temperature is generally preferred in order to promote substantially complete conversion within the above noted time ranges.

The process proceeds through a dimer-like compound of the Formula III



25 This dimer-like compound is produced within about 1 hour to about 3 hours upon mixing the imine of Formula I with an aminopyridine of the formula



However, continued stirring, especially at elevated temperatures of about 60°C to about 100°C, results in complete conversion of the dimer-like compound to the desired compound of Formula II. The dimer-like compound of Formula III generally is reacted with an aminopyridine in situ, thus avoiding isolation. The compound can be isolated, however, if desired.

The final product of the process, a compound of Formula II, is readily isolated by simply filtering the reaction mixture and washing the precipitate with a solvent such as water, or an acid such as 6N hydrochloric acid followed by a wash with an organic solvent such as acetonitrile or methanol. Alternatively, the reaction mixture can first be concentrated, for example by evaporation of the reaction solvent under reduced pressure, and the mixture can be suspended in a solvent such as ethyl acetate or ethanol, filtered, and again washed with water, or a weak acid, followed by a wash with an organic solvent. The solid product generally is dried in a vacuum oven at about 30°C to about 50°C.

If desired, the product of Formula II can be further purified by routine processes such as chromatography, recrystallization from solvents such as DMSO, or it can be converted to a pharmaceutically acceptable acid addition salt.

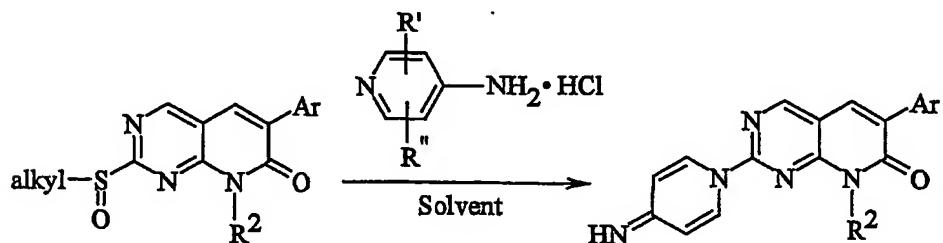
Pharmaceutically acceptable acid addition salts of the compound of Formula II include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate,

-10-

methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977;66:1-19).

5 The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise, the salts are 10 equivalent to their respective free base for purposes of the present invention.

15 The starting material required for the present process is a 2-(4-imino-4H-pyridin-1-yl)-pyrido[2,3-d]pyrimidine of Formula I. This starting material can be prepared by reacting a 2-alkylsulfinyl-pyrido[2,3-d]pyrimidine with a 4-aminopyridine. The 2-alkylsulfinyl compound is available as described in United States Patent No. 5,733,914. The 2-alkylsulfinyl-pyrido[2,3-d]pyrimidine is reacted with an equimolar or excess of 4-aminopyridine, generally as an acid addition salt, as follows:



20 The reaction generally is carried out in an organic solvent such as acetonitrile, tetrahydrofuran, or the like, and generally is substantially complete within about 2 to 10 hours when carried out at an elevated temperature of about 30°C to about 80°C. The product of Formula I is readily isolated as an acid addition salt by simply filtering the reaction mixture and drying it, either in an oven or in open air.

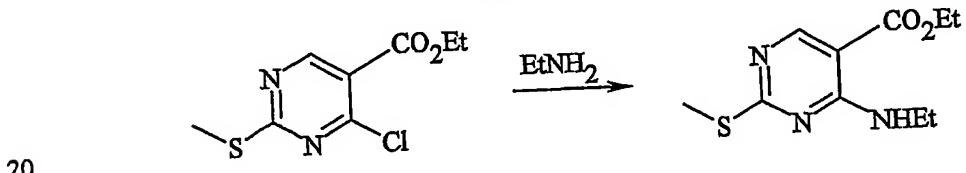
25 As noted above, the 2-alkylsulfinyl-pyrido[2,3-d]pyrimidines are available by the process described in United States Patent No. 5,733,914. That process comprises reacting an aryl acetonitrile with a 2-alkylsulfanyl-4-alkylamino-pyrimidine-5-carboxaldehyde to produce the corresponding 2-alkylsulfanyl-

-11-

pyrido[2,3-d]pyrimidine, followed by oxidation to the sulfoxide (a 2-alkylsulfinyl-pyrido[2,3-d]pyrimidine). A further embodiment of this invention is an improved process for making the initial 2-alkylsulfanyl intermediate that comprises reacting an arylacetic acid ester (instead of an aryl acetonitrile) with a 2-alkylsulfanyl-4-alkylamino-pyrimidine-5-carboxaldehyde. The reactants are generally mixed in approximately equimolar quantities in an unreactive organic solvent and in the presence of a coupling reagent such as 1,8-diazabicyclo[5.4.0]undec-7-ene. The reaction is generally complete within about 1 to 8 hours when carried out at an elevated temperature of above 40°C to about 100°C. The product, 2-alkylsulfanyl pyridopyrimidine, is readily isolated by filtration. This process affords surprisingly better yields and improved purity compared to that described in United States Patent No. 5,733,914. The 2-alkylsulfanyl pyridopyrimidine is readily oxidized to the corresponding 2-alkylsulfinyl derivative by reaction with normal oxidation agents such as m-chloroperbenzoic acid or *trans*-2-phenylsulfonyl-3-phenyl-oxaziridine.

15 The following detailed examples further illustrate the process of this invention. The examples are provided as illustration only, and are not intended to limit the invention in any respect.

PREPARATION 1



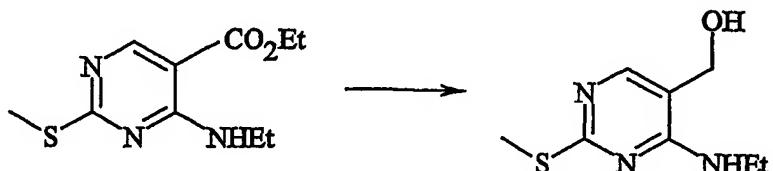
4-Ethylamino-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester

25 A 22-L, 4-necked round-bottomed flask was equipped with a mechanical stirrer, a dropping funnel, and a thermometer. The flask was charged with the ethyl 4-chloro-2-(methylthio)-5-pyrimidinecarboxylate (1.53 kg, 6.56 mol), triethylamine (2.74 L, 19.7 mol, 3 eq), and 7.5 L of tetrahydrofuran to give a solution. The aqueous ethylamine (0.53 L, 6.56 mol, 1 eq) was added via the dropping funnel over 20 minutes. The reaction temperature rose to 35°C during the addition. The reaction was stirred at ambient temperature for 2 hours. The reaction was checked for completion using TLC (SiO₂; 7:3/heptane:ethyl acetate).

-12-

The precipitate (triethylamine hydrochloride) was filtered off and washed 2 times with tetrahydrofuran, combining the washes with the original filtrate. The tetrahydrofuran was stripped to near dryness on a rotary evaporator. The residue was partitioned between saturated aqueous sodium bicarbonate (500 mL) and ethyl acetate (1 L). Note that there is carbon dioxide gas evolution from the bicarbonate both during the partitioning and the subsequent washes. The layers were separated and the organic layer washed 2 times with saturated aqueous sodium bicarbonate and 1 time with brine. The solution was dried over magnesium sulfate, filtered, and stripped to give the titled compound as an off-white solid. Yield: 95%.

PREPARATION 2



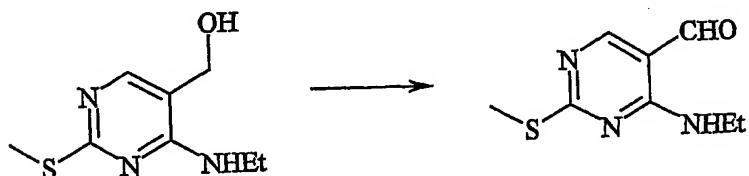
4-Ethylamino-2-methylsulfanyl-pyrimidin-5-yl-methanol

The 50-L built-in reactor was purged with argon 3 times, and then a positive argon pressure was maintained throughout the process. The reactor was charged with 4 L of tetrahydrofuran, followed by lithium aluminum hydride (1 M in tetrahydrofuran, 6.77 kg, 7.48 L, 7.48 mol, 1.2 eq). The chiller/heater was set to 18°C and activated. The product of Preparation 1, 4-ethylamino-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.5 kg, 6.23 mol, 1 eq), was dissolved in 11 L of tetrahydrofuran (0.58 M) and was added to the reaction vessel using a pump over ~2 hours. TLC (SiO₂; 7:3/heptane:ethyl acetate) was used to monitor the reaction for completion. When the reaction was complete, the chiller/heater was set to 10°C. The excess hydride was quenched by adding successively: 1.25 L of water, 1.25 L of 15 wt% sodium hydroxide, and then 4.1 L of water. The first portion of water was added quite slowly and with vigorous stirring to keep down the foaming and to keep the temperature below 30°C. As the quench continues, the addition rate was gradually increased until the final portion of water could be added in a steady stream. The reaction mixture was then stirred for 1 hour before

-13-

filtering through a 1-inch plug of celite in a 2 L coarse fritted funnel. The salts were washed once with tetrahydrofuran on the funnel. The tetrahydrofuran was stripped, then the residue azeotroped 2 times with 1 L portions of toluene. The resulting solid was washed from the flask using heptane, then dried in a vacuum oven at 40°C to give the titled compound which is used in the next step without further purification.

PREPARATION 3

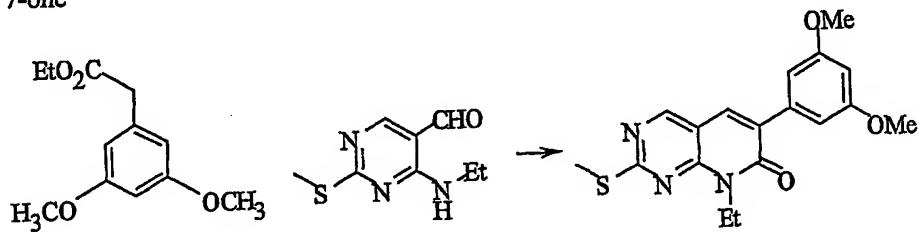


10 4-Ethylamino-2-methylsulfanyl-pyrimidine-5-carboxaldehyde

A 50-L round-bottomed flask equipped with a mechanical stirrer was charged with 565 g (2.84 mol) of the product of Preparation 2, 4-ethylamino-2-methylsulfanyl-pyrimidin-5-yl)-methanol, 1.23 kg (14.2 mol, 5 eq) of manganese (IV) oxide, and 19 L of chloroform. The mixture was stirred 24 hours at room temperature, then checked by TLC (SiO_2 ; 7:3/heptane:ethyl acetate) for completion of reaction. The reaction was filtered through a plug of celite and the chloroform stripped to give the titled compound in 90% yield.

EXAMPLE 1

20 2-Methylsulfanyl-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one



-14-

A 5-L round bottomed flask was charged with 516 g (2.62 mol) of 4-ethylamino-2-methylsulfanyl-pyrimidine-5-carboxaldehyde, 587 g (2.62 mol) of (3,5-dimethoxy-phenyl)-acetic acid ethyl ester, and 391 mL (2.62 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was heated at 80°C for one hour. Thin layer chromatography (TLC) (silica, 6:4/heptane:ethyl acetate, developed in an iodine chamber) showed all the 4-ethylamino-2-methylsulfanyl-pyrimidine-5-carbaldehyde was consumed. Ethyl alcohol (absolute, 2.75 L) was added to the reaction vessel, and the reaction mixture was cooled to room temperature. The solid that precipitated was collected by filtration, washed once with ethyl alcohol, and dried in a vacuum oven at 45°C for 12 hours to provide 530 g (57% yield) of 2-methylsulfanyl-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one. Proton NMR (DMSO) is consistent with the structure: ¹H NMR (DMSO): δ 8.86 (s, 1H), 8.10 (s, 1H), 6.83 (d, 2H), 6.51 (s, 1H), 4.36 (q, 2H), 3.75 (s, 1H), 2.58 (s, 3H), 1.22 (t, 3H). The combined mother liquor and washes were allowed to stand at room temperature for seven days. At this time a second crop of precipitate was collected, washed once with ethyl alcohol, and dried in a vacuum oven at 45°C for 12 hours to provide 79 g (8.5% yield) of 2-methylsulfanyl-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one. Proton NMR (DMSO) is consistent with the structure.

20

EXAMPLE 1A

2-(Methylsulfanyl)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]-pyrimidine-7-one
4.8 kg of 4-ethylamino-2-methylsulfanyl-pyrimidine-5-carboxaldehyde and 5.5 kg of (3,5-dimethoxyphenyl)-acetic acid ethyl ester were dissolved in 10 L of DMSO at room temperature and stirred. 4.4 kg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added to the reaction mixture. The mixture was heated at about 45-50°C for at least 3 hours. The reaction was monitored by reverse-phase HPLC (YMC-AQ column, 60:40 CH₃CN/0.02 M SDS, pH 2.2, 1.0 mL/min, 254 nm). When the reaction was completed, ethyl alcohol (3 L) was added to the reaction vessel, which was cooled to 5-15 °C. The yellow product was precipitated and collected by filtration, washed with a mixture of isopropyl alcohol and water (3 L + 3 L),

-15-

and dried in a vacuum tray dryer at about 40-45 °C for at least 12 hours using a house vacuum (~30 in Hg) to provide 7.3 kg (84% yield) of 2-(methylsulfanyl)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one. Proton NMR is consistent with the structure.

5 EXAMPLE 2

2-Methylsulfinyl-6-(3,5-dimethoxy-phenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of 2-methylsulfanyl-6-(3,5-dimethoxy-phenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one (17.0 g, 0.048 mol) in CHCl₃ (150 mL), was added 10 *trans*-2-phenylsulfonyl-3-phenyloxaziridine (15.2 g, 0.058 mol; Organic Synthesis, 1987; 66:203-210). The reaction mixture was stirred overnight at room temperature. The product was purified by filtering through a large sintered glass funnel filled with silica gel wetted with CHCl₃. The product was eluted off the silica gel with the following order of solvents: CHCl₃, EtOAc, MeOH/CHCl₃ (1:20), and MeOH/CHCl₃ (1:10). The solvent was removed under reduced pressure and the residue taken up in hot EtOAc (40 mL, 50°C), filtered, and concentrated to 20 mL by evaporation under reduced pressure. The product precipitated and was collected by filtration to give 13.77 g of the titled compound, mp 114-116°C.

15 Alternatively, To a solution of the product of Example 1 or 1A, (536.2 g, 20 1.50 mol) in CHCl₃ (3.4 L), was added *trans*-2-phenylsulfonyl-3-phenyloxaziridine (431 g, 1.65 mol; Organic Synthesis, 1987; 66:203-210). The reaction mixture was stirred overnight at room temperature. Methyl t-Butyl Ether (MTBE) was added to the solution until a precipitate formed (~7 L). The solid was 25 collected by filtration, washed once with MTBE and dried in a vacuum oven at room temperature. Proton NMR (DMSO) is consistent with the structure.

EXAMPLE 3

2-(4-Imino-4H-pyridin-1-yl)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride

30 To a solution of 220 g (0.59 mol) of the product of Example 2, 2-methylsulfinyl-6-(3,5-dimethoxy-phenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-

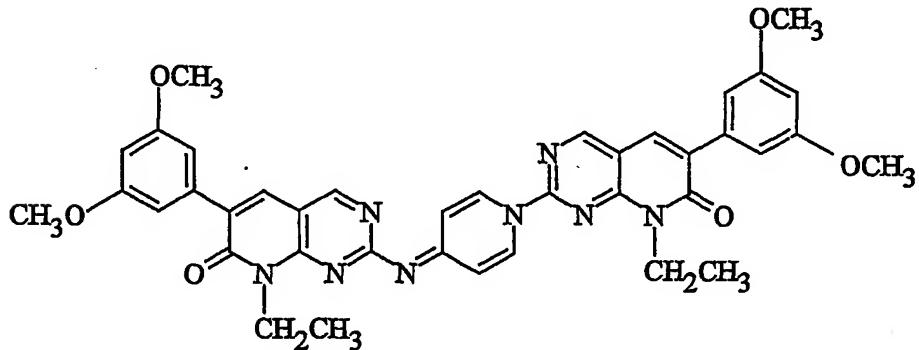
-16-

7-one, in 2 L of acetonitrile was added a solution of 100 g (0.765 mol, 1.3 eq) of 4-aminopyridine hydrochloride in 700 mL of ethanol. The mixture was heated to 40°C and stirred for 6 hours. The mixture was then cooled to 24°C and filtered to provide 256 g (99%) of 2-(4-imino-4H-pyridin-1-yl)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride; mp 295-300°C (dec).

EXAMPLE 4

2-(Pyridin-4-ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one

To a stirred solution of 330 g (0.75 mol) of 2-(4-imino-4H-pyridin-1-yl)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride in 1.5 L of dimethylsulfoxide were added in one portion 114 g (0.825 mol) of powdered potassium carbonate, followed by the addition of a solution of 2.8 g (0.03 mol; 0.05 eq) 4-aminopyridine in 50 mL of dimethylsulfoxide. The reaction mixture was heated to 100°C, and aliquots were removed after 1 hour and analyzed by reverse phase high pressure liquid chromatography (RP-HPLC) (YMC-AQ column, 60:40 CH₃CN/0.02 M SDS, pH 2.2, 1.0 mL/min, 254 nm). After 40 minutes, the reaction was shown to produce the title compound, plus a dimer-like compound of the formula



The foregoing dimer-like compound is named 2-{4-(6-[3,5-dimethoxyphenyl]-7-oxo-8-ethyl-8H-pyrido[2,3-d]pyrimidine-2-yl)-imino)-4H-pyridin-1-yl}-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one.

The reaction mixture was stirred at 100°C for a total of 60 hours, at which time RP-HPLC revealed that all dimers had been converted to 2-(pyridin-4-

-17-

ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one. The reaction mixture was cooled to 45°C and acidified by addition of 300 mL of 6N hydrochloric acid (the acidification was exothermic). The acidic solution was stirred for 4 hours at 24°C, during which time the product had precipitated as a 5 bright yellow solid. The precipitate was filtered and washed with 200 mL of 6N hydrochloric acid, with 250 mL of water, with 800 mL of acetonitrile, and finally with 300 mL of methyl tert-butyl ether. The precipitate was dried in a vacuum oven at 40°C for 12 hours to provide 303 g (92% yield) of 2-(pyridin-4-ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride; mp 295-300°C (dec). Mass Spec (APCI) 439.89 m/z..

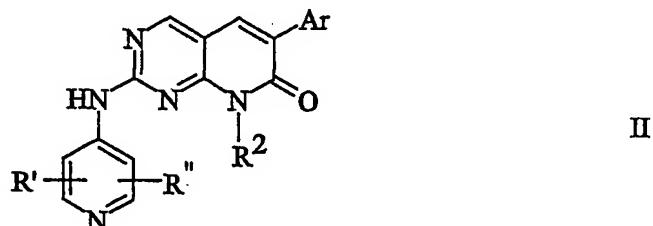
10 The hydrochloride salt was reacted with 1N sodium hydroxide to provide 2-(pyridin-4-ylamino)-6-(3,5-dimethoxyphenyl)-8-ethyl-8H-pyrido[2,3-d]pyrimidine-7-one free base: mp 305-307°C. Mass Spec (APCI) 403.9 m/z.

-18-

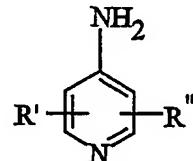
CLAIMS

What is claimed is:

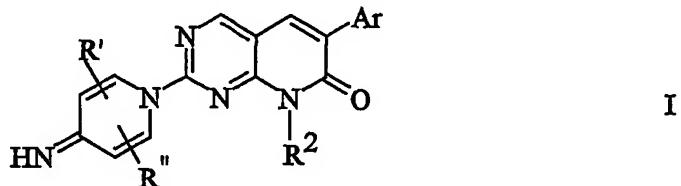
1. A process for preparing a 2-(pyridin-4-ylamino)-pyrido[2,3-d]pyrimidine of Formula II



comprising reacting a 4-aminopyridine of the formula



with a 2-(4-imino-4H-pyridin-1-yl)-pyrido[2,3-d]pyrimidine of Formula I



10 in the presence of a base:

wherein

R' and R'' independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or phenyl;

15 R² is (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; heteroaromatic, cycloalkyl, C₁-C₆ alkyl, and C₂-C₆ alkenyl, where the alkyl and alkenyl groups may be substituted by NR₅R₆, phenyl, substituted phenyl, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl,

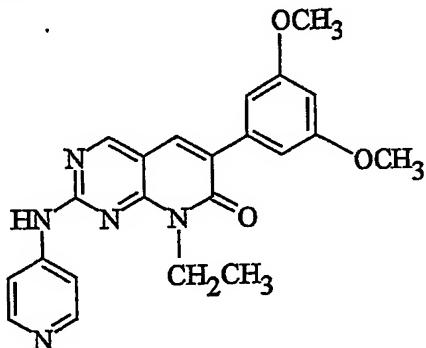
-19-

heteroaromatic, and R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur; and

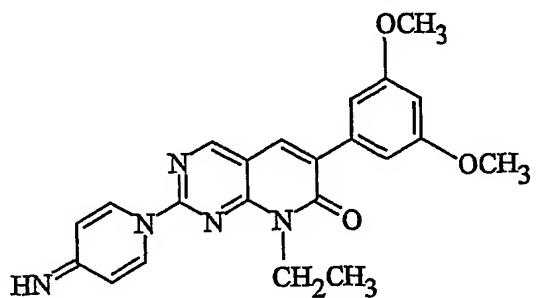
5

Ar is phenyl, substituted phenyl, or heteroaromatic.

2. A process according to Claim 1 wherein Ar is substituted phenyl.
3. A process according to Claim 1 wherein Ar is di-C₁-C₆ alkoxy phenyl.
4. A process according to Claim 1 wherein R² is C₁-C₆ alkyl.
- 10 5. A process according to Claim 1 wherein R' and R'' both are hydrogen.
6. A process for preparing a compound of the formula



comprising reacting 4-aminopyridine with a compound of the formula

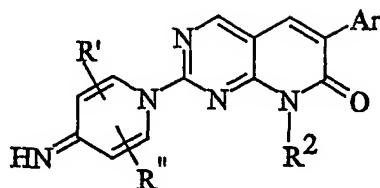


15

in the presence of a base.

-20-

7. A compound of the Formula I



I

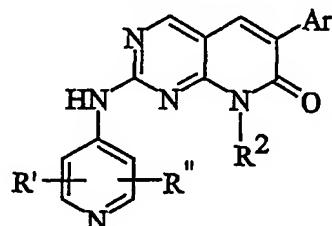
wherein:

Ar is phenyl, substituted phenyl, or heteroaromatic;

5 R' and R'' independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or phenyl; andR² is (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2,or 3; heteroaromatic, cycloalkyl, C₁-C₆ alkyl, and C₂-C₆ alkenyl, where the alkyl and alkenyl groups may be substituted by NR₅R₆,10 phenyl, substituted phenyl, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur.

15

8. A process for preparing a compound of Formula II



II

20

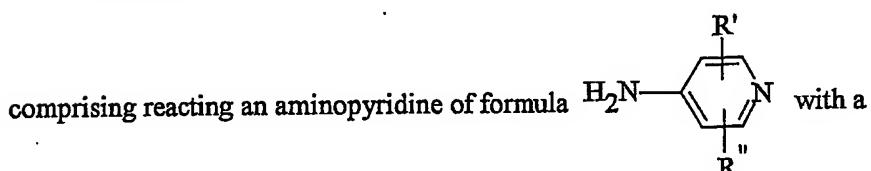
wherein:

Ar is phenyl, substituted phenyl, or heteroaromatic;

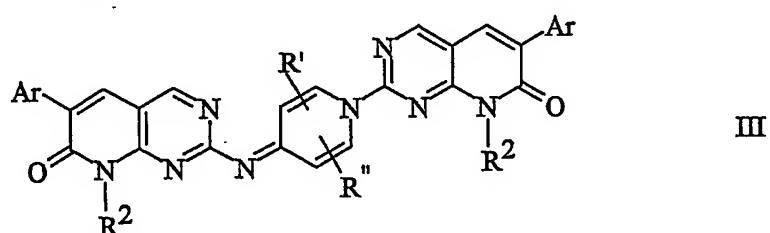
R' and R'' independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or phenyl; and

-21-

R^2 is $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; heteroaromatic, cycloalkyl, C_1 - C_6 alkyl, and C_2 - C_6 alkenyl, where the alkyl and alkenyl groups may be substituted by NR_5R_6 , phenyl, substituted phenyl, cycloalkyl, and where R_5 and R_6 are independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, $(CH_2)_nPh$ where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and R_5 and R_6 taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur

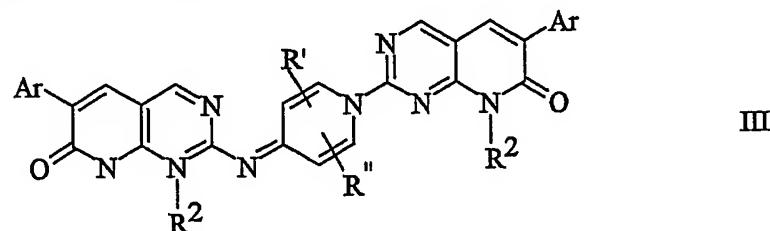


compound of Formula III



15 in an unreactive organic solvent.

9. A compound of Formula III



wherein:

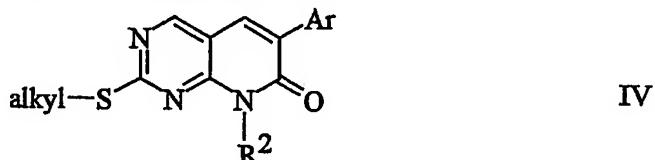
Ar is phenyl, substituted phenyl, or heteroaromatic;

-22-

R' and R'' independently are hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or phenyl; and

R² is hydrogen, (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; heteroaromatic, cycloalkyl, C₁-C₆ alkyl, and C₂-C₆ alkenyl, where the alkyl and alkenyl groups may be substituted by NR₅R₆, phenyl, substituted phenyl, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur.

10. A process for preparing a 2-alkylsulfanyl pyridopyrimidine of Formula IV



wherein:

Ar is phenyl, substituted phenyl, or heteroaromatic; and

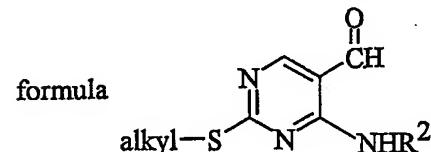
R² is hydrogen, (CH₂)_nPh, where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; heteroaromatic, cycloalkyl, C₁-C₆ alkyl, and C₂-C₆ alkenyl, where the alkyl and alkenyl groups may be substituted by NR₅R₆, phenyl, substituted phenyl, cycloalkyl, and where R₅ and R₆ are independently C₁-C₆ alkyl, C₂-C₆ alkenyl, (CH₂)_nPh where Ph is phenyl or substituted phenyl, and n is 0, 1, 2, or 3; cycloalkyl, heteroaromatic, and R₅ and R₆ taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or

-23-

3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur comprising reacting an aryl

acetic acid ester of the formula $\text{alkyl}-\text{O}-\overset{\text{O}}{\underset{||}{\text{C}}}-\underset{\text{Ar}}{\text{CH}_2}$ with a 2-

alkylsulfanyl-4-alkylamino-pyrimidine-5-carboxaldehyde of the



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

(10) International Publication Number
WO 02/12237 A3

PCT

(51) International Patent Classification⁷: C07D 471/04, 519/00 // (C07D 471/04, 239:00, 221:00) (C07D 519/00, 471:00, 471:00)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(21) International Application Number: PCT/US01/22001

(22) International Filing Date: 12 July 2001 (12.07.2001)

(25) Filing Language: English

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

(30) Priority Data:
60/223,084 4 August 2000 (04.08.2000) US

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(71) Applicant (for all designated States except US):
WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(88) Date of publication of the international search report:
10 May 2002

(72) Inventors; and

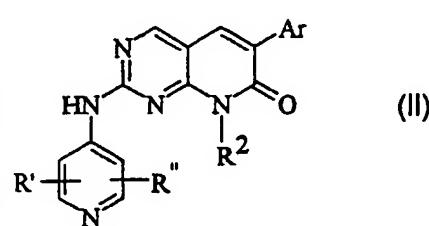
(75) Inventors/Applicants (for US only): BEYLIN, Vladimir Genukh [US/US]; Pfizer PGDR, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). LEE, Richard, Jungkyu [US/US]; Pfizer Holland Chemical Development, 188 Howard Avenue, Holland, MI 49423 (US). MARLATT, Mark, Eugene [US/US]; Pfizer PGDR, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: FEDERMAN, Evan, J. et al.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/12237 A3

(54) Title: PROCESS FOR PREPARING 2-(4-PYRIDYL)AMINO-6-DIALKYLOXYPHENYL-PYRIDO[2,3-D]PYRIMIDIN-7-ONES



(57) Abstract: Process for preparing 2-pyridylamino-pyrido[2,3-d]pyrimidines of Formula (II) wherein Ar is aryl, R' and R'' are hydrogen, alkyl, alkoxy, or phenyl, and R² is alkyl.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 01/22001A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D519/00 // (C07D471/04, 239:00, 221:00),
(C07D519/00, 471:00, 471:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Cat->vv	Character of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 733 914 A (BLANKLEY CLIFTON JOHN ET AL) 31 March 1998 (1998-03-31) cited in the application columns 17-20, scheme IV examples 65-68, 93 column 11, line 64 -column 12, line 62; examples 65-67	1-9
X	-----	10

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *g* document member of the same patent family

Date of the actual completion of the international search

5 March 2002

Date of mailing of the international search report

14/03/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/22001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5733914	A 31-03-1998	US 5620981 A	15-04-1997
		AU 713727 B2	09-12-1999
		AU 5576996 A	21-11-1996
		BG 62617 B1	31-03-2000
		BG 102003 A	30-12-1998
		CA 2214219 A1	07-11-1996
		CN 1183099 A	27-05-1998
		CZ 9703275 A3	18-03-1998
		EE 9700274 A	15-06-1998
		EP 0823908 A1	18-02-1998
		HU 9801704 A2	30-11-1998
		IL 117923 A	01-06-2000
		JP 11504922 T	11-05-1999
		NO 975033 A	31-10-1997
		PL 323089 A1	02-03-1998
		SK 141097 A3	08-07-1998
		WO 9634867 A1	07-11-1996
		ZA 9603486 A	13-11-1996

